

Metaphysical Games: An Imaginary Lecture on Crafting Earth's Biological Future

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IN RETROSPECT, I REALIZE THAT IT WAS WITH SOME RELUCTANCE that I had accepted the commission to compose a futuristically oriented presentation. In part, had I not used up a self-imposed lifetime quota that goes back over nearly 50 years? In part, it might expose questionable error or redundancy in the exercise. Was there anything more to be said that had not been explored many times over? Molecular biotechnologies had reached such a state of potential power that there might be no limit to the possible. Did that need further recitation? It then occurred to me that however problematic the product, there might be merit in a process (call it a game) that would stretch my own imagination, and that of readers.

Designs for the Future

Futures over a period of decades are not strictly limited or determined by today's technological maps—rather, they will be a product of current accomplishments and proximate outgrowths from these; limits imposed by laws of physics and chemistry; personal and collective decisions about setting priorities for investment; social decisions about what to regulate; and extraordinary personal creativity in the above-set environments.

In short, the future awaits being made, not revealed. My aim is to invite informed debate about what to seek in the designs for the future, and then how to shape technologies (and vice versa), and carefully anticipate what gains, hazards, precautions, and regulations might attend success in those aims—an extension of technology assessment. Such technology assessment might bear on enhancing creative focus on what should be done as much as or more than what is proscribed.

This is entirely a call to scrutinize, not insist on what will or should be undertaken. Nevertheless, it is inescapable that DNA sequence-related technologies will be expanded at an explosive pace. The more difficult tasks of translating sequence data into physiological interventions are still just dimly within reach, and are more likely to be accomplished sensibly if the challenges are articulated.

Mirroring how the human genome project eventually prevailed, this proposal for the 21st century is to (1) button down the DNA sequence of every species of discernible in-

terest; (2) identify every gene; and (3) design genomic interventions that will optimize each genetic pathway. Needless to say, the bulk of the actual work will be robotized. The expression "genes to order" epitomizes how easy it is now to originate a new species; its annotations will be grace notes remarking on the largest and smallest, fastest and most ponderous, beastie of its kind. The scenarios define some uses of laboratory procedures to scramble hitherto immured physiological pathways now that species boundaries are a "real world" curiosity.

Defer the critical triage of execution until the uses and means have been clearly and widely thought about. Please keep it clear: this dialectic is the latent purpose of the game. The game becomes interesting when it forces thinking about unfamiliar conjunctions—the mouse, sized like the bacterium in microns, or in turn like the fruit fly in millimeters. What, indeed, are the ultimate limits to size of different phylogenetic constructions? Playing the combinatorial game, what could a bacterium-sized mouse mean? For the sake of this exercise, size stands for any of a whole array of physiological adjustments in this platform.

The primate genome is a banner already unfurled. For the 21st century, it might read "sequencing all terrestrial genomes," hence biodiversity at its limit. For the 22nd century, consider systematic samples of new and artificial trait combinations with more behavioral enhancements than anyone could dare think about for the time being.

There is equal regard for what can be harvested from nature and what is gleaned by the new art. Investigators will be impatient for news about microcephaly in animals, the converse of the enlarged brain. This is another instance in which clinical interest in large human populations has uncovered genes that could then be followed up in animals.

For this thought project, the focus is on genomic intervention. There is yet another universe of environmental modulations; those are euphenic and are left for another day.

Future Traits and Bioengineering Concepts

A vector of traits can be plucked from natural sources, or constructed with present or proximate future bioengineering tools (BOX). Taken without question is the ultimate ca-

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Box. Traits That Could Be the Foundation of Selection in Unfamiliar Genomic Settings

Fecundity. This is the fundamental measure of Malthusian fitness. Is obviously the most complex of traits, and rarely given fully unhampered play except in natural or near-natural populations. It may also be entangled with efficiencies of diet, infection, and social arrangements. The race is not always to the swift, paradoxical selection sometimes favors a slower-growing contender, with antibiotics that are more effective on bugs that have lowered their guard during the most rapid growth. What is the fastest-growing microbe? Perhaps a cousin of *Vibrio natriegens*, with a doubling time of less than 15 minutes.

Life span. Research in this part of the matrix is well filled in yeast, roundworms, fruit flies, mice, birds—for these species constitute a large part of the research agenda of the National Institute of Aging.

Chemical secretion, defense, detection, virulence, or disease susceptibility. What substance? What toxin? What function? Recall that secondary metabolism comprises a large part of contemporary applied microbiology.

Desiccation. Survival and growth capacity of cells at reduced chemical activity of water. This is closely connected with anabiosis and dormancy with explicit or tacit spore formation. Large investments by the National Aeronautics and Space Administration are wrapped up with this issue because it is generally argued that the surface environment of Mars is incompatible with proliferation of terrestrial microbes. Depending on process details, the process of lyophilization may be toxic or preservative. Additives like trehalose mitigate the toxicity of the lyophilization process and may be emulated by other genetically engineered antifreeze under extensive investigation. Persistence of viable bacteria in aerosols is a critical point for a biological weapons attack.

Motor. Power and discriminatory skills; motility some specialized cells. Some flagella are imputed to rotate at 50 000 rpm!

Flight, marine, navigation kinetic fragility/tenacity. One aspect testable with acoustic energy in environment. Converse, more limited range in animals but what is loudest emission, doubtless related to animal size. For smaller targets this is tested by aerosolization.

Thermal-susceptibility. Easily assayed, and heat/cold shock responses are under study.

Thermal emission and absorption. Should be secondary to metabolic rates.

Tropisms. To any part of *em spectrum*: what are ultimate limits to sensitivity of detection?

Vision-spatial acuity. Image formation at any wavelength.

Energy emissions. May carry acoustic signals. Luminescence may be acoustically modulated, detected.

Integration of signal inputs: IQ. It involves coordinated social action. As an outrageous question, "What could be measured, say in a bacterium, that could map to what might be called 'intelligence'?"

Geno-stability and pheno-stability (or instability); promiscuity. This trait may be related to survivability of laboratory cultures, to maintenance of strain characteristics, to production of variants as objects of selection, and to ease of research protocols.

Genome size. An interesting trait in itself; related to "junk DNA."

Currency of lateral gene transfer. Bears on management of genetic change.

capacity to craft altered and hybrid genomes—"knockouts," "knockins," "knockdowns and knockups," and "shuffles." Augmenting these constructions is the deconstruction of what is disappointing, what does not work as predicted. Mock or denounce, but get the arguments into the open for the feasibility and utility of constructing or domesticating a target candidate. At some point, there will be exhilaration or unease about the policy fallout, and colleagues will be consulted about the best avenues for technology assessment.

Orthogonal to the traits is a vector of organisms, which may range from microbes to plants, roundworms to orangutans, supporting the plea to conserve all of these special evolutionary outcomes, even including (with great care) pathogens that have threatened human health. The deconstruction of their special relationship to humans is a great challenge that will not be consummated for some years to come, campaigns to "burn the bugs" notwithstanding. I refrain from inscribing the bestiary, the entries are common knowledge. Some colleagues have built their careers on developing such laboratory artifacts as individualized strains

of *Escherichia coli*, roundworms, the white mouse, fruit flies, the macaque, . . . the list goes on.¹

Scattered entries of this matrix with specialized functionalities are then already being pursued diligently (eg, extremophile projects that focus on natural microbes living on the edge of supporting habitats). Can thermophilia or psychrophilia be exported to mesophyllic bacteria, or to fruit flies, or to mice? If not, why not, is the perennial question that exposes the reductive explanations.

Study of life at the edge has been institutionalized, notably by the International Society for Extremophiles. There is even some fun to be had in following through the even "dumber" more systematic filling of the matrix. For example, consider "size" and mammals. Monod² already suggested to look more deeply at elephants in his discussion of "what is true for *E coli* is true for the elephant." That may have been falsified in nontrivial ways. It does lead to asking: what is the smallest mammal? Answer: the pigmy shrew (*Suncus etruscus*; weighs 2 g). What is the smallest primate? Answer: pygmy mouse lemur (*Microcebus myoxi-*

nus; weighs 30 g). Likewise, what is the largest bacterium? Answer: an enteric symbiont in the surgeonfish, dimensionally larger than 0.1 mm.³

Then what does limit the size of an organism? How can every organ retain a viable coordination of its parts at every stage of fetal as well as embryonic development? Early post-natal development is perhaps the most challenging: what are the statistics over a range of species to exhibit the emergence of individual autonomy?

And then there are the possibilities of futuristic elves. For instance, if elves could be domesticated (and if not, why not?), they might be handy laboratory models for forensic, physiological, pharmacological, or toxicological studies. The last proposal might fail as many would protest that the differential adaptations needed to live in a mouse-sized world probably outweigh the similitudes evoked by "primate" or "mammal" but these suppositions require closer inspection. Then exactly why must a primate, at the limit, be so much larger than the nonprimate cousin? Could the shrew's genome be stretched to give flylike dimensions? Moreover, one might posit the design of animals with smaller or larger livers, kidneys, immune systems, spleens, hearts, somatic musculature, or brains. Does enhanced social intelligence go along with larger brains? The perennial question will be: if the corresponding genes are activated in situ or transplanted to yeast or corn, what then? Scientists are no longer startled by the natural conservation of many gene families across a broad reach of eukaryotes.

The utilities of a minified animal like *C. rhabditis* have been well demonstrated. How does its metabolism compare with that of a historically larger animal? Will its cultivability match that of other vermin?

Most of the traits listed are already under study in some organism, whether at the microlevel or at the mega level. How does the presentation herein differ from any of a multitude of projects? It is a multitude of projects, the head-

ings reminding the reader of the many and diverse parts. But these would be reintegrated into a more coherent whole. If for a moment it were to be taken as a serious proposal, it might engulf the total research budgets of the engaged academies. Serious attention needs to be given again to process, starting with consensus as needed. The agenda should involve (1) what to seek, (2) how to get there, (3) how does it work, and (4) what are the hazards and precautions?

This discussion has been inordinately focused on individual organisms, ignoring communities as actors, bar their (bugs') occasional sweeps in epidemics around the globe. Think about how the bugs coordinate their own counter-efforts.

This exercise has been strenuous, as I played the game at its inception. It started, obviously, partly in jest, with the expectation that quite serious business would emerge. What disaster might arise when we invent and promulgate a new jungle frontier—smart bushmeat! If small, smart primates do succeed rodents, will they also displace them as pets, as reservoirs of arthropod-borne viruses? Will they be so easy to manage? There already have been alarm bells from the outbreak of squirrel-borne monkeypox in 2003.⁴ Again and again, what started out with the semblance of science fiction turned out to be close to if not a fully realized technology—like green fluorescent protein markers for differential gene expression. Who knows where and how it will all end.

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